# Umbilical cord lactate compared with pH as predictors of intrapartum asphyxia

ADRIAN NEACSU[1,2*], CĂTĂLIN GABRIEL HERGHELEGIU[1,3], SILVIU VOINEA[4*],
MIHAI CORNEL TRAIAN DIMITRIU[1,5], LIANA PLES[1,6], ROXANA ELENA BOHILTEA[1,7],
ANCA DANIELA BRAILA[8], LEONARD NASTASE[1,3], NICOLAE BACALBASA[1,9],
LAURA IOANA CHIVU[1,10], FLORENTINA FURTUNESCU[11*] and RALUCA GABRIELA IOAN[1,3]

[1]Department of Obstetrics and Gynecology, 'Carol Davila' University of Medicine and Pharmacy, 020021 Bucharest;
[2]Department of Obstetrics and Gynecology, 'Sf. Ioan' Emergency Clinical Hospital, 042122 Bucharest;
[3]Department of Obstetrics and Gynecology, 'Alessandrescu-Rusescu' National Institute for Healthcare of Mother and Child,
020395 Bucharest; [4]Department of Surgery, Institute of Oncology 'Prof. Dr. Alexandru Trestioreanu', 020122 Bucharest;
[5]Department of Obstetrics-Gynecology, 'Sf. Pantelimon' Emergency University Hospital, 021623 Bucharest;
[6]Department of Obstetrics and Gynecology, Bucur Maternity Hospital, 012361 Bucharest; [7]Department of Obstetrics
and Gynecology, University Emergency Hospital Bucharest, 050098 Bucharest; [8]Department of Obstetrics and Gynecology,
University of Medicine and Pharmacy of Craiova, 200349 Craiova; [9]Department of Obstetrics and Gynecology,
'I. Cantacuzino' Clinical Hospital, 030167 Bucharest; [10]Department of Pathophysiology, 'Carol Davila'
University of Medicine and Pharmacy, 020021 Bucharest; [11]Department of Public Health and Management,
Faculty of Medicine, 'Carol Davila' University of Medicine and Pharmacy, 050463 Bucharest, Romania

**Abstract.** Despite advances in fetal monitoring during labor, one of the most critical causes of neonatal death and neurologic injuries remains intrapartum asphyxia. Umbilical cord gases can be used to detect acidosis and fetal distress. We conducted a retrospective, multicenter study to evaluate umbilical cord blood pH and lactate as a mean of evaluating the degree of intrapartum hypoxia and also to establish which of the two is more reliable in predicting morbidity in term neonates. The present study utilized a total of 124 cases that met the criteria for intrapartum asphyxia and 150 normal term newborns that were randomly selected as case control. Both umbilical cord lactate and pH proved to be accurate predictors of neonatal morbidity caused by intrapartum hypoxia. Lactate proved to be superior to pH in predicting adverse neonatal outcome. The greatest sensibility and specificity in predicting intrapartum asphyxia were achieved in our study by using a cutoff value of 3.75 mmol/l for lactate and 7.24 for pH.

## Introduction

Despite the advances in fetal monitoring during labor, one of the most critical causes of neonatal death and neurologic injuries remains intrapartum asphyxia (IA) (1-4). During labor and birth, IA leads to hypoxia and fetal acidosis. Thus, a reliable method for detecting acidosis can be a useful tool for predicting adverse neonatal outcome due to IA (2,5-7).

Acidosis can be evaluated and it is defined as low umbilical cord pH or high umbilical base deficit (expressed as negative base excess, BE) at birth (7-9). Hypoxia due to impaired blood supply to the fetus leads in the early stages to respiratory acidosis that is characterized by a decrease in pH but normal BE. Following these initial events, if hypoxia continues there will be a shift to anaerobic metabolism, resulting in the formation of lactic acid and increase in BE (6,8,9). Thus, high cord blood lactate levels can be correlated with fetal acidosis and asphyxia (10,11).

Some studies suggest that neonatal complications are associated with metabolic acidosis, rather than respiratory acidosis, thus a distinction between the two is important for predicting those neonate at risk for morbidity and mortality (6,12). Because lactate is a direct end product of anaerobic metabolism it can be used to differentiate between metabolic and respiratory acidosis. Furthermore, some studies suggest that the measurement of umbilical cord blood lactate is more accurate

*Correspondence to:* Dr Cătălin Gabriel Herghelegiu or Professor Roxana Elena Bohiltea, Department of Obstetrics and Gynecology, 'Carol Davila' University of Medicine and Pharmacy, Bd. Eroii Sanitari 8, 020021 Bucharest, Romania
E-mail: cnr_cata@yahoo.com
E-mail: r.bohiltea@yahoo.com

*Contributed equally

than pH measurements in predicting neonatal outcome (10,13). Since labor and birth can be complicated by a wide variety of events such as retroplacental hematoma, prematurity, and dystocia, it is important to be able to objectively confirm or infirm intrapartum hypoxia (12-14).

Perinatal hypoxia is difficult to predict and avoid, as it can be the result of fetal malformations, prematurity, labor dystocia or unexpected events such as retroplacental hematoma (14,15). In addition, in some cases even less severe pathologies such as thrombophilia can be an important risk factor for perinatal hypoxic events (16-18). Thus, an objective mean of assessing fetal hypoxia is important for confirming or excluding intrapartum asphyxia and predicting neonatal long term morbidity and mortality (19,20).

We conducted a retrospective, multicenter study to evaluate umbilical cord blood pH and lactate as a mean of evaluating the degree of intrapartum hypoxia and also to establish which of the two is more reliable in predicting morbidity in term neonates. This study continues and extends the research previously carried out by Mogos *et al* at a single center (7).

## Patients and methods

*Newborns*. Our study included newborns born between 2010 and 2012 in three hospitals in Romania: INSMC 'Alessandrescu Rusescu', Bucur Maternity Hospital and Craiova Emergency Hospital. The information was gathered from the archived patient medical records and included gestation age, fetal heart rate monitoring during labor, birth weight, Apgar score, umbilical blood gases (pH and lactate) and neonatal outcome. The data collected retrospectively did not contain personal information and only the agreements of the ethics committee of the participant hospitals were required and obtained without the need of informed consent or the consent of the patient/legal representative in the case of minors.

We included in the intrapartum asphyxia group (IA) all newborns from term singleton births with markers of a severe hypoxic event during labor defined as the presence of at least one of the following: Severe changes in fetal heart rate (<100, >160), meconium staining and in the presence of at least one of the following: Low Apgar score (≤3 in the first minute or ≤5 after 5 min); respiratory failure (defined/characterized as absence of spontaneous breathing after more than 5 min or mechanical ventilation for more than 10 min); the need for intensive care unit admission for more than 24 h.

The exclusion criteria for the IA group were: Encephalopathy determined by causes other than IA, congenital malformations, congenital metabolic diseases, viral infection, septic shock, major organ failure, or fetal trauma during birth.

A control group of 150 healthy newborns from term singleton births, that did not meet any of the above criteria (IA or exclusion), and that had information regarding umbilical cord gases, was randomly selected from the newborn that were registered between 2010 and 2012.

Term pregnancy was defined as a gestational age of 37 weeks or greater and only singleton pregnancies were selected.

Receiver operating characteristics (ROC) curves were constructed to evaluate the predictive value of pH and lactate for fetal asphyxia and neonatal death. To objectively compare

Table I. pH and lactate values in the IA and control groups.

| Variable | IA group (n=124) | Control group (n=150) |
|---|---|---|
| pH | 7.17±0.07 (7.05-7.32) | 7.28±0.06 (7.13-7.38) |
| Lactate (mmol/l) | 5.34±1.5 (2.35-8.75) | 2.78±0.7 (1.25-4.35) |

Data are expressed as mean ± SD (range). P<0.001, IA group compared with the control group. IA, intrapartum asphyxia.

the predictive characteristic of pH and lactate we used the maximal Youden index to determine the 'optimal' cutoff value for each variable. The Youden index takes into account sensitivity and specificity and it is used to estimate the diagnostic effectiveness of different cutoff values (19).

*Statistical analysis*. The data were collected using Office-Excel version 14.7.7 and for the statistical analysis NCSS 2019 Statistical Software (2019) (NCSS, LLC.; ncss.com/software/ncss) was used. The characteristics for each group were calculated using 'Descriptive statistics'. The variables were compared using two sample t-test. The results were analyzed and interpreted according to the obtained P-value; P<0.05 was considered to be statistically significant.

## Results and discussion

During the period 2010-2012 there were 21,224 births; a total of 124 cases met our criteria for IA. The umbilical cord pH was significantly lower (P<0.001) in the IA group, with a mean of 7.17 with values ranging between 7.05 and 7.32, compared to a mean of 7.28 for the Control group (Table I, Fig. 1). In addition, the lactate values were significantly higher (P<0.001) for the IA group, with a mean of 5.34 mmol/l and values ranging between 2.35 and 8.75 mmol/l, compared to a mean of 2.78 mmol/l for the Control group (Table I, Fig. 1).

The ROC curves for lactate and pH for evaluating IA are shown in Fig. 2. The pH had a ROC curve area of 0.75, while the lactate had a ROC curve area of 0.92; thus, lactate was significantly more accurate in predicting IA. Judging by the maxim Youden index, the optimal cutoff value was 7.24 for pH with an index of 0.62 and 3.75 mmol/l for lactate with an index of 0.70 (Table II). Both sensitivity and specificity were higher for lactate compared to pH (87.1 and 83.2% compared to 86.3 and 74.0%).

Umbilical cord gases represent one of the most objective ways to evaluate newborn metabolic status and rule out perinatal asphyxia (21,22). In our study, the results confirm that increased umbilical cord blood lactate is an accurate predictor of neonatal morbidity due to intrapartum asphyxia. By comparing the ROC curve areas, lactate proved to be superior to pH in predicting poor neonatal outcome. In addition, although there are numerous proposals for cutoff values of pH and lactate to be used for confirming IA and predicting a poor outcome (23,24), the greatest sensitivity and specificity were achieved in our study by using a cutoff value of 7.24 for pH and 3.75 mmol/l for lactate (Table II).

There are two possible explanations for which lactate appears to be superior in predicting neonatal morbidity and

Table II. Sensitivity and specificity of the different cutoff values for pH and lactate for evaluating IA.

| Variable | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|
| pH | | |
| ≤7.12 (10th percentile) | 31.4% (23.4-40.4) | 99.9% (97.5-100) |
| ≤7.17 (mean IA value) | 50.8% (41.6-59.8) | 93.3% (88.1-96.7) |
| ≤7.24 ('optimal cutoff' from the ROC curve) | 86.3% (78.9-91.8) | 74.0% (66.2-80.8) |
| Lactate (mmol/l) | | |
| ≥7.00 (90th percentile) | 27.4% (19.7-36.1) | 99.9% (97.5-100) |
| ≥5.35 (mean IA value) | 48.4% (39.3-57.5) | 98.6% (95.2-99.8) |
| ≥3.75 'optimal cutoff' from the ROC curve | 87.1% (79.8-92.4) | 83.2% (76.3-87.5) |

IA, intrapartum asphyxia; CI, confidence interval; ROC, receiver operating characteristics.
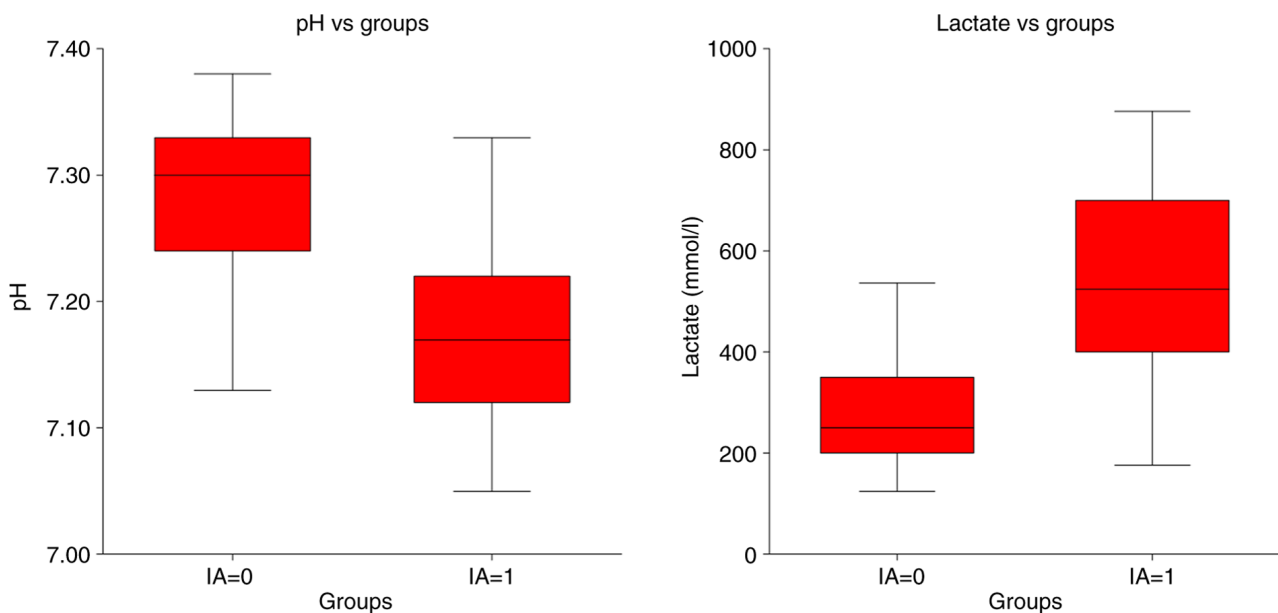


Figure 1. Box plots for pH and lactate values in the IA and Control groups. IA=1, control group; IA=1, IA group; IA, intrapartum asphyxia.
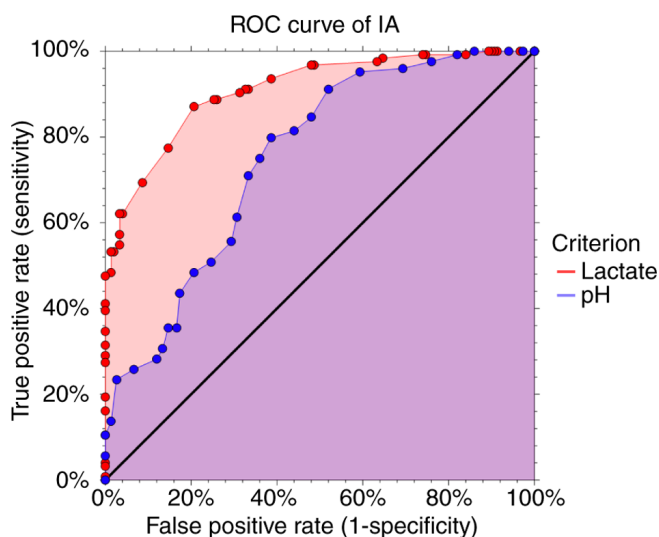


Figure 2. Receiver operating characteristic (ROC) curves of pH and lactate for the diagnosis of IA. IA, intrapartum asphyxia.

mortality. First of all, lactate is a direct product of anaerobic metabolism; thus, it is produced earlier during hypoxia. Therefore, changes in its value occur and can be detected more rapidly than low pH (25,26). Secondly, high umbilical cord blood lactate is a specific marker of metabolic acidosis which is associated with more neonatal complications than respiratory acidosis (6,12).

As with premature births, we are still far from being able to predict and avoid intrapartum asphyxia, despite the efforts made over the last decades (27). As technology progresses, probably more and more sensors and intelligent textiles will be developed, that will be able to detect fetal hypoxia and distress before severe lesions occur. Yet, until that time, evaluating cord blood gases remains one of the most reliable ways of detecting but also excluding fetal hypoxia (20,28,29). Moreover, in today's era of defensive medicine and prenatal diagnostics, it is important to rule out IA as a contributing cause for the poor neurological outcome of neonates diagnosed prenatally with complex malformations such

as holoprosencephaly, Galen vein aneurism or other brain anomalies (30-35).

In 2014, the American College of Obstetricians and Gynecologists compiled a summary of all specified signs present in the neonatal period and all the factors that suggest or lead to a diagnosis as early as possible of an acute perinatal hypoxic-ischemic event (36). The first neonatal sign is an Apgar score below 5 at 5 and 10 min, which then is followed by fetal acidemia in the umbilical artery with a pH <7.0 or the presence of base deficit ≥12 mmol/l, separately or together. Furthermore, the impact of IA can be observed by imaging trough magnetic resonance imaging or spectroscopy where acute brain injuries can be noted (37,38). The next sign of certainty is the presence of hypoxic-ischemic encephalopathy and multisystem organ failure. Early detection of these signs may limit the progression to irreversible consequences (39).

One limitation of our study was that it included only term neonates thus the results may not be valid for preterm births. Moreover, only short-term outcome was taken into consideration. Thus, future studies may be needed to assess the predictive ability of pH and lactate for long-term outcomes and in cases of premature birth.

In conclusion, both umbilical cord lactate and pH can be used as accurate predictors of neonatal morbidity caused by intrapartum hypoxia, as it has been showed in numerous studies. Our study confirmed that lactate is superior to pH in predicting adverse neonatal outcome. The greatest sensitivity and specificity in predicting IA were achieved in our study by using a cutoff value of 3.75 mmol/l for lactate and 7.24 for pH. For these cutoff values, the sensitivity and specificity for lactate were 87.1 and 83.2%, while for pH they were 86.3 and 74.0%.

## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Authors' contributions

AN, REB and CGH collected, analyzed and interpreted the patient data. SV, MCTD and LP collected the data and had substantial contribution to the conception of the research and statistical analysis. ADB, LN and NB substantially contributed to the conception of the study, the interpretation of the data and the writing of the manuscript. LIC and RGI contributed to the literature retrieval and manuscript modification. AN, REB and FF supervised and designed the present study and contributed to the approval of the final version of the manuscript. All authors read and approved the final version of the manuscript.

## Ethics approval and consent to participate

The data collected retrospectively did not contain personal information and only the agreement of the ethics committee of INSMC 'Alessandrescu Rusescu' Bucharest, Bucur Maternity Hospital Bucharest and Craiova Emergency Hospital were required and obtained without the need of informed consent or the consent of the patient/legal representative in the case of minors.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

## References

1. Freeman JM and Nelson KB: Intrapartum asphyxia and cerebral palsy. Pediatrics 82: 240-249, 1988.
2. Omo-Aghoja L: Maternal and fetal acid-base chemistry: A major determinant of perinatal outcome. Ann Med Health Sci Res 4: 8-17, 2014.
3. Schifrin BS and Ater S: Fetal hypoxic and ischemic injuries. Curr Opin Obstet Gynecol 18: 112-122, 2006.
4. Ahearne CE, Boylan GB and Murray DM: Short and long term prognosis in perinatal asphyxia: An update. World J Clin Pediatr 5: 67-74, 2016.
5. Graham EM, Ruis KA, Hartman AL, Northington FJ and Fox HE: A systematic review of the role of intrapartum hypoxia-ischemia in the causation of neonatal encephalopathy. Am J Obstet Gynecol 199: 587-595, 2008.
6. Ross MG and Gala R: Use of umbilical artery base excess: Algorithm for the timing of hypoxic injury. Am J Obstet Gynecol 187: 1-9, 2002.
7. Mogos M, Herghelegiu CG, Ioan RG, Cringu AI and Neacsu A: Determining an umbilical cord pH cutoff value for predicting neonatal morbidity related to intrapartum hypoxia. Rev Chim 70: 605-607, 2019.
8. Fahey J and King TL: Intrauterine asphyxia: Clinical implications for providers of intrapartum care. J Midwifery Womens Health 50: 498-506, 2005.
9. Victory R, Penava D, da Silva O, Natale R and Richardson B: Umbilical cord pH and base excess values in relation to adverse outcome events for infants delivering at term. Am J Obstet Gynecol 191: 2021-2028, 2004.
10. Gjerris AC, Stær-Jensen J, Jørgensen JS, Bergholt T and Nickelsen C: Umbilical cord blood lactate: A valuable tool in the assessment of fetal metabolic acidosis. Eur J Obstet Gynecol Reprod Biol 139: 16-20, 2008.
11. Bohîlţea RE, Zugravu CA, Neacsu A, Navolan D, Berceanu C, Nemescu D, Bodean O, Turcan N, Baros Al and Cîrstoiu MM: The prevalence of vitamin D deficiency and its obstetrical effects. A prospective study on Romanian patients. Rev Chim 70: 1228-1233, 2019.
12. Goldaber KG, Gilstrap LC III, Leveno KJ, Dax JS and McIntire DD: Pathologic fetal acidemia. Obstet Gynecol 78: 1103-1107, 1991.
13. Tuuli MG, Stout MJ, Shanks A, Odibo AO, Macones GA and Cahill AG: Umbilical cord arterial lactate compared with pH for predicting neonatal morbidity at term. Obstet Gynecol 124: 756-761, 2014.
14. Brăila AD, Krastev BM, Mihai-Zamfir E, Caraveţeanu DC, Al Krayem N, Brăila M, Velea R and Neacşu A: Uteroplacental apoplexy associated with invasive cervical neoplasm. Rom J Morphol Embryol 58: 1465-1470, 2017.
15. Brăila AD, Gluhovschi A, Neacşu A, Lungulescu CV, Brăila M, Vîrcan EL, Cotoi BV and Gogănău AM: Placental abruption: Etiopathogenic aspects, diagnostic and therapeutic implications. Rom J Morphol Embryol 59: 187-195, 2018.
16. AbdelAziz NH, AbdelAzeem HG, Monazea EM and Sherif T: Impact of thrombophilia on the risk of hypoxic-ischemic encephalopathy in term neonates. Clin Appl Thromb 23: 266-273, 2017.

17. Bohîlțea R, Turcan N, Ionescu C, Toader O, Nastasia S, Neculcea D, Movileanu I, Munteanu O and Cîrstoiu M: The incidence of prematurity and associated short-term complications in a multidisciplinary emergency hospital from Romania. In: Proceedings of the 5th Romanian Congress of the Romanian Society of Ultrasound in Obstetrics and Gynecology, pp105-112, 2017.

18. Braila AD, Neacsu A, Musetescu AE, Vircan EL, Florescu A and Bumbea AM: BIochemical markers in pregnancy associated with Sjogren's syndrome and thrombophilia. Rev Chim 69: 2300-2303, 2018.

19. Youden WJ: Index for rating diagnostic tests. Cancer 3: 32-35, 1950.

20. Depp R: Perinatal asphyxia: Assessing its causal role and timing. Semin Pediatr Neurol 2: 3-36, 1995.

21. Turcan N, Bohiltea RE, Ionita-Radu F, Furtunescu F, Navolan D, Berceanu C, Nemescu D and Cirstoiu MM: Unfavorable influence of prematurity on the neonatal prognostic of small for gestational age fetuses. Exp Ther Med 20: 2415-2422, 2020.

22. Turcan N, Bohîlțea R, Neacsu A, Baros Al and Cîrstoiu MM: The role of anticoagulant therapy in the prevention of preeclampsia. Pharmacokinetic and pharmacodinamic mechanisms. Rev Chim 70: 1424-1428, 2019.

23. Bohîlțea RE, Cîrstoiu MM, Ionescu CA, Niculescu-Mizil E, Vlădăreanu AM, Voican I, Dimitriu M and Turcan N: Primary myelofibrosis and pregnancy outcomes after low molecular-weight heparin administration: A case report and literature review. Medicine (Baltimore) 96: e8735, 2017.

24. Bohiltea RE, Zugravu CA, Nemescu D, Turcan N, Paulet FP, Gherghiceanu F, Ducu I and Cirstoiu MM: Impact of obesity on the prognosis of hypertensive disorders in pregnancy. Exp Ther Med 20: 2423-2428, 2020.

25. Hamed HO: Intrapartum fetal asphyxia: Study of umbilical cord blood lactate in relation to fetal heart rate patterns. Arch Gynecol Obstet 287: 1067-1073, 2013.

26. Ionescu AC, Popescu I, Banacu M, Matei A, Bohîlțea R and Dimitriu M: Is it possible to predict stillbirth in the third trimester? Filodiritto Editore-Proceedings. In: Proceedings of the 5th Romanian Congress of the Romanian Society of Ultrasound in Obstetrics and Gynecology, pp194-198, 2017.

27. Engidawork E, Chen Y, Dell'Anna E, Goiny M, Lubec G, Ungerstedt U, Andersson K and Herrera-Marschitz M: Effect of perinatal asphyxia on systemic and intracerebral pH and glycolysis metabolism in the Rat. Exp Neurol 145: 390-396, 1997.

28. Neacsu A, Calin A, Braila AD, Navolan DB, Dimitriu M, Stanica CD, Ioan R and Ionescu C: Chemical effects and predictive factors in premature birth. Rev Chim 69: 1796-1801, 2018.

29. Cummins G, Kremer J, Bernassau A, Brown A, Bridle HL, Schulze H, Bachmann TT, Crichton M, Denison FC and Desmulliez MPY: Sensors for Fetal Hypoxia and Metabolic Acidosis: A Review. Sensors (Basel) 18: 2648, 2018.

30. Onose G, Chendreanu C, Neacsu A, Grigorean V, Strâmbu V, Toader C, Spânu A, Ioana A, Anghelescu A, Onose L, Haras M, et al: Smart textiles for noninvasive monitoring of physiological signals. Ind Textila 60: 124-133, 2009.

31. Herghelegiu CG, Duta SF, Neacsu A, Suciu N and Veduta A: Operator experience impact on the evaluation of still images of a first trimester cardiac assessment protocol. J Matern Neonatal Med 1-5, 2020.

32. Ionescu CA, Calin D, Navolan D, Matei A, Dimitriu M, Herghelegiu C and Ples L: Alobar holoprosencephaly associated with a rare chromosomal abnormality. Medicine (Baltimore) 97: e11521, 2018.

33. Herghelegiu D, Ionescu CA, Pacu I, Bohiltea R, Herghelegiu C and Vladareanu S: Antenatal diagnosis and prognostic factors of aneurysmal malformation of the vein of Galen: A case report and literature review. Medicine (Baltimore) 96: e7483, 2017.

34. Ionescu CA, Vladareanu S, Tudorache S, Ples L, Herghelegiu C, Neacsu A, Navolan D, Dragan I and Oprescu DN: The wide spectrum of ultrasound diagnosis of holoprosencephaly. Med Ultrason 21: 163-169, 2019.

35. Domingues AP, Moura P and Vieira DN: Obstetric litigation: The importance of the quality of clinical files and its influence on expertise conclusions. J Obstet Gynaecol (Lahore) 35: 146-149, 2015.

36. Executive summary: Neonatal encephalopathy and neurologic outcome, second edition. Report of the American College of Obstetricians and Gynecologists' Task Force on Neonatal Encephalopathy. Obstet Gynecol 123: 896-901, 2014.

37. Munteanu O, Cîrstoiu MM, Filipoiu FM, Bohîlțea R, Brătilă E, Bulescu IA and Berceanu C: Morphological and ultrasonographic study of fetuses with cervical hygroma. A case series. Rom J Morphol Embriol 57: 1421-1427, 2016.

38. Iacob RE, Iacob D, Moleriu RD, Tit DM, Bungau S, Otrisal P, Aleya S, Judea-Pusta C, Cioca G, Bratu OG, et al: Consequences of analgesics use in early pregnancy: Results of tests on mice. Sci Total Environ 691: 1059-1064, 2019.

39. Bohîlțea R, Furtunescu F, Turcan N, Navolan D, Ducu I and Cîrstoiu M: Prematurity and intrauterine growth restriction: Comparative analysis of incidence and short term complication. Proceedings of SOGR 2018. In: Proceedings of the 17th National Congress of The Romanian Society of Obstetrics and Gynecology 2018, pp708-712, 2019.